producing cells *in vitro* comprising introducing into the cell a dominant negative allele of a *PMS2*, wherein the dominant negative allele encodes a truncated PMS2 that consists of the first 133 amino acids of PMS2; and (2) a homogeneous culture of isolated, hypermutable antibody-producing cells as described for the method claims. The Office Action alleges that the claims are not commensurate with the scope of the disclosure, such that undue experimentation would be necessary to make and use the invention. Applicants respectfully traverse.

Much of the discussion in the Office Action regarding enablement is drawn to the issue of claims reading on *in vivo* application of the methods and transgenic animals. Without conceding the correctness of the rejection as it may apply to *in vivo* applications of the method or transgenic animals in any continuation or divisional applications, Applicants have amended the method claims in the instant application to include the feature that he method is performed *in vitro*, as helpfully suggested by the Examiner. The Applicants have also amended the claims to the cells in the instant application, as helpfully suggested by the Examiner, to include the feature that the cells are isolated. According to the Office Action (Paper No. 20, page 13) these amendments to the method claims and the cell claims obviates the enablement rejection with respect to reading on *in vivo* methods and transgenic animals, respectfully. Therefore, Applicants request withdrawal of the rejection under 35 U.S.C. §112, first paragraph, on these grounds.

With respect to the other forms of truncation mutants than strictly those consisting of the first 133 amino acids of PMS2, the Applicants believe the Examiner's position is unduly narrow with respect to what is enabled by the Specification for the following reasons, and respectfully urge the Examiner to reconsider.

The Office Action alleges that the Applicants have failed to provide evidentiary support that there is no undue experimentation required to practice the claimed invention as claimed.

The Office Action's asserts that the Specification provides no more than a "plan" or "invitation" to experiment (see Office Action of Feb. 26, 2003, Paper No. 20, page 11, citing *Enzo Biochem, Inc. v. Calgene Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999)).

In the Office Action, the Examiner cites *Enzo* which states:

> Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment practicing antisense in eukaryotic cells; they do not provide sufficient guidance or specificity as to how to execute that plan (Citations omitted). As we stated in *Genentech* [*Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2D (BNA) 1001, 1005]:
>
> "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

The Court noted in Footnote 10:

> In view of the rapid advances in science, we recognize that what may be unpredictable at one point in time may become predictable at a later time. See *Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2D (BNA) at 1445 ("We do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification.").

Thus, each application under examination is entitled to an independent evaluation as to whether the field of the invention is "unpredictable." The Examiner appears to conclude that the area of experimentation is in an unpredictable art based on the teachings of Ngo

et al. in THE PROTEIN FOLDING PROBLEM AND TERTIARY STRUCTURE PREDICTION, Merz et al., (eds.), 1994 (hereinafter "Ngo").

Ngo discusses algorithms to determine a protein's three-dimensional structure based solely on amino acid sequence (see Ngo *et al.*, page 492, paragraph 2, line 1: "It is not known whether there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence ***alone***") (emphasis added). However, the Specification is not dealing with predicting structure-functional relationship based on an amino acid sequence alone. The function of the mismatch repair protein *is known*. The amino acid sequences of the various PMS2 mismatch repair proteins *are known*. The homology between PMS2 sequences *is known*. Thus, there is a level of predictability among the types of alterations of PMS2 sequences that may result in a dominant negative effect. Moreover, the types of alterations that have been demonstrated to have an effect are not subtle changes, involving the substitution of one amino acid for another. Rather, truncation mutants deleting a substantial portion of the C-terminus of PMS2 confers the dominant negative phenotype.

The prior art teaches that PMS2 is highly conserved at the N-terminus, containing five regions of conserved exons which encompass the PMS2-134 truncated domain (Nicolaides *et al.* (1995) "Genomic Organization of the Human *PMS2* Gene Family" *Genomics* 30:195-206; figure 5E ("Nicolaides I")). The highly conserved nature of this area of the PMS2 protein indicates that there is a known structure associated with the protein. Moreover, functional domains are known for PMS2. For example, it was known in the art that the carboxyl-terminus of PMS2 was responsible for binding MLH1 in the mismatch repair complex (Nicolaides *et al.* (1998) "A Naturally Occurring *hPMS2*

Mutation Can Confer a Dominant Negative Mutator Phenotype" *Mol. Cell. Biol.* 18(3):1635-1641; page 1640, first full paragraph ("Nicolaides II")). A truncation mutant would obviously not allow interaction with MLH1. Nicolaides II also teaches that the conserved N-terminus may interact with and inhibit a downstream component of the mismatch repair complex (*e.g.*, a nuclease) (Nicolaides II at page 1640, first full paragraph). Thus, it was recognized in the art that the N-terminus of PMS2 is highly conserved and the art had ascribed a functionality to the deleted portion of PMS2-134 and the conserved portion encompassed by hPMS2-134.

The Specification also provides clear guidance in the form of detailed experiments which could be carried out on a routine basis for determining other dominant negative mutants. A great deal of experimentation is permitted before the law considers the experimentation "undue" – particularly where the experimentation is clear and routine. We invite the Examiner's attention to the Specification at page 25, Example 2, wherein a method for screening for dominant negative mutants is taught. Briefly a reporter gene system is described wherein microsatellite instability (the hallmark of a mismatch repair defect) is rapidly identified upon transfection of a construct containing a candidate dominant negative mutant. This assay may be used on a routine basis to identify additional PMS2 dominant negative truncation mutants without undue experimentation. Thus, the Applicants provide substantially more than a mere "wish" or "invitation" to experiment.

Thus, given the teachings of the Specification and the knowledge in the prior art, one of skill in the art would not doubt that the various truncations encompassing the N-

terminal portion of PMS2, when expressed, would have a dominant negative effect on mismatch repair. Thus, the Specification enables the use of dominant negative PMS2.

2. Written Description

The Office Action rejects claims 1, 2, 4, 9-11, 22, 23, 25, 29, and 73-80 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description. Applicants respectfully traverse the rejection.

In a recent Federal Circuit decision, *Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc. v. Diamond Automation, Inc.* 2003 U.S. App. LEXIS 6285 (Fed. Cir. 2003), the Federal Circuit discussed the written description requirement at length. The Federal Circuit explained that its own case law shows two primary goals in the written description requirement. The first is embodied in its decision in *In re Wertheim* 541 F.2d 257, 191 USPQ 90 (CCPA 1976), and the second is embodied in its decision *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The *Wertheim* court noted that "the function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter *later* claimed by him." *Wertheim* at 541 F.2d 257, 262, 191 USPQ 90, 96. As restated more recently by the Federal Circuit:

> The purpose of the written description requirement is to prevent an applicant from *later* claiming that he invented that which he did not; the applicant for a patent is therefore required "to recount his invention in such detail that his *future claims can be determined to be encompassed within his original creation.*"

Amgen Inc. v. Hoechst Merion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (emphasis added)).

The second goal of the written description requirement, was addressed in *Regents of the University of California v. Eli Lilly & Co.* The *Eli Lilly* court applied the written description requirement to adequacy of a description of a DNA sequence. The court held that a precise definition of the DNA sequence was required to satisfy the written description requirement, even in the absence of priority issues. The court has further refined this rule in such cases as *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1069 (Fed. Cir. 2002) and *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). In *Amgen*, the Federal Circuit clarified its holding in *Eli Lilly*, stating: "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure." *Amgen Inc. v. Hoechst Merion Roussel Inc.*, 314 F.3d at 1332. Moreover, a representative number of species within a claimed genus may fulfill the written description requirement. *The Regents of the University of California v. Eli Lilly and Company* 119 F.3d 1559, 1568 (Fed. Cir. 1997).

The subject claims, as amended, do not go beyond the scope of the claims as originally filed, and thus satisfy the first goal of the Written Description Requirement that the Applicants were in possession of the claimed invention (*i.e.*, there is no issue of later claiming).

Further, the Applicants have satisfied the second goal of the written description requirement by showing that "the disclosed function is sufficiently correlated to a known, particular structure." That is, the Applicants have provided a demonstration that truncation mutants of PMS2 proteins, when expressed in the cells, exert a dominant negative effect. As more fully discussed above, Applicants demonstrated that a dominant negative form of the PMS2 protein, PMS2-134, exerts a dominant negative effect on cells. The specification further describes a mouse PMS2 which is highly homologous to human PMS2. The Applicants described the full scope of the invention, providing a functional description sufficiently correlated with a particular known structure to show that they were in possession of the invention.

The Examiner's reliance on Ngo *et al.* is misplaced. Ngo discusses algorithms to determine a protein's three-dimensional structure based solely on amino acid sequence (see Ngo *et al.*, page 492, paragraph 2, line 1: "It is not known whether there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone"). However, the Specification is not dealing with predicting structure-functional relationship based on an amino acid sequence alone. The function of the protein *is known*. The amino acid sequence of the protein *is known*. The homology of the sequences *is known*. Thus, Ngo is irrelevant to the inquiry. It is not necessary for the applicants to show detailed predicted three-dimensional structure, or crystalization data of all homologs in order to satisfy the written description requirement. Applicants have provided an actual reduction to practice, relevant identifying characteristics of the primary amino acid sequences of PMS2 genes, coupled with an art-recognized structural-functional relationship of PMS2 domains and functionality in mismatch repair (note that

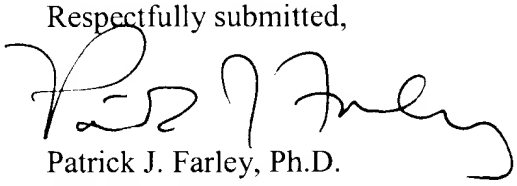
the two Nicolaides references cited in this response were explicitly incorporated by reference in the application at page 20, lines 34-35 and reference numbers 16 and 24). These characteristics are sufficient to show one of skill in the art that the inventors were in possession of the invention at the time of filing.

Applicants earnestly submit that the Written Description Requirement is fulfilled with respect to the amended claims, and respectfully urge withdrawal of the rejection of claims 1, 2, 4, 9-11, 22, 23, 25, 29, and 73-80 under 35 U.S.C. §112, first paragraph.

CONCLUSION

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,



Patrick J. Farley, Ph.D.
Reg. No. 42,524

Date: July 28, 2003

Morphotek Inc.
210 Welsh Pool Road
Exton, PA 19341
Tel. (610) 423-6146
Fax (610) 423-6199

BACKFILE DOCUMENT INDEX SHEET

A DOCPHOENIX

APPL PARTS

_____ IMIS ____
Internal Misc. Paper

_____ LET. ____
Misc. Incoming Letter

_____ 371P ____
PCT Papers in a 371Application

_____ A... ____
Amendment Including Elections

_____ ABST ____
Abstract

_____ ADS ____
Application Data Sheet

_____ AF/D ____
Affidavit or Exhibit Received

_____ APPENDIX ____
Appendix

_____ ARTIFACT ____
Artifact

_____ BIB ____
Bib Data Sheet

_____ CLM ____
Claim

_____ COMPUTER ____
Computer Program Listing

_____ CRFL ____
All CRF Papers for Backfile

_____ DIST ____
Terminal Disclaimer Filed

_____ DRW ____
Drawings

_____ FOR ____
Foreign Reference

_____ FRPR ____
Foreign Priority Papers

_____ IDS ____
IDS Including 1449

_____ NPL ____
Non-Patent Literature

_____ OATH ____
Oath or Declaration

_____ PET. ____
Petition

_____ RETMAIL ____
Mail Returned by USPS

_____ SEQLIST ____
Sequence Listing

_____ SPEC ____
Specification

_____ SPEC NO ____
Specification Not in English

_____ TRNA ____
Transmittal New Application

OUTGOING

_____ CTMS ____
Misc. Office Action

_____ 1449 ____
Signed 1449

_____ 892 ____
892

_____ ABN ____
Abandonment

_____ APDEC ____
Board of Appeals Decision

_____ APEA ____
Examiner Answer

_____ CTAV ____
Count Advisory Action

_____ CTEQ ____
Count Ex parte Quayle

_____ CTFR ____
Count Final Rejection

_____ CTNF ____
Count Non-Final

_____ CTRS ____
Count Restriction

_____ EXIN ____
Examiner Interview

_____ M903 ____
DO/EO Acceptance

_____ M905 ____
DO/EO Missing Requirement

_____ NFDR ____
Formal Drawing Required

_____ NOA ____
Notice of Allowance

_____ PETDEC ____
Petition Decision

INCOMING

_____ AP.B ____
Appeal Brief

_____ C.AD ____
Change of Address

_____ N/AP ____
Notice of Appeal

_____ PA.. ____
Change in Power of Attorney

_____ REM ____
Applicant Remarks in Amendment

7-28-03 XT/ 1
Extension of Time filed separate

Internal

_____ SRNT ____
Examiner Search Notes

_____ CLMPTO ____
PTO Prepared Complete Claim Set

_____ ECBOX ____
Evidence Copy Box Identification

_____ WCLM ____
Claim Worksheet

_____ WFEE ____
Fee Worksheet

File Wrapper

_____ FWCLM ____
File Wrapper Claim

_____ IIFW ____
File Wrapper Issue Information

_____ SRFW ____
File Wrapper Search Info

REV 7/02/03